REMARKS

Claims 12-19, 24-39, 43-47, 50-59, and 62-63 are pending in the application. Claims 12-19, 24-29, 40 and 43-45 have been withdrawn from further consideration. Claims 30-39, 46-47, 50-59, and 62-63 have been examined on the merits. Accordingly, no new matter has been inserted into the application. No new issue has been raised requiring further search or consideration.

Rejection Under 35 U.S.C. § 103(a) Over Hellmann in view of Moon, LaPlante, Hu '062 (U.S. Patent No. 6,107,062), and Gewirtz (Proc. Natl. Acad. Sci. 1996. v. 93, pp. 3161-3163)

Claims 22, 23, 30-39, 41, 42, and 46-61 have been rejected as being obvious over Hellmann in view of Moon, LaPlante, Hu '062 and Gewirtz. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Hellmann

Hellmann discloses an M13 molecule with a Tobacco Vein Mottling Virus (TVMV) insert sequence. Hellmann further discloses performing DNA:RNA hydridization assays with the M13 molecule in a reticulocyte lysate cell-free translation system, the so called hybrid-arrested translation system.

Hellmann fails to disclose or suggest mixing the M13 molecule with a transfection effective composition containing lipids such as cationic lipids or liposomes because Hellmann's assays with the M13 molecule is conducted entirely in a cell-free system, and there is no disclosure or suggestion found in Hellmann to include any cell transfection reagent for introducing the M13 molecule into a eukaryotic cell.

Moon

Moon discloses a ribbon-type antisense oligonucleotide of about 120 nucleotides mixed with a transfection reagent.

LaPlante

LaPlante discloses transfecting a cell with cDNA that expresses mRNA encoding CHERP.

Hu '062

Hu '062 discloses a cell-based system for inhibiting target gene expression in which the cells are transfected with a double-stranded plasmid.

Gewirtz

Gewirtz discloses that lipid transfection agents can be mixed with oligodeoxynucleotides and plasmid DNA.

Distinctions of the present invention over the cited references

Basic considerations which apply to obviousness rejections

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). (MPEP 2141).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant"s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). MPEP 2142.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in

the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). MPEP 2143.

In order to establish *prima facie* obviousness of the invention over the cited references, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced a number of decisions overturning obviousness rejections due to a lack of suggestion in the prior art of the desirability of combining references, as discussed in the aforementioned section. In the present situation, the Examiner has failed to establish *prima facie* obviousness of the present invention over Hellmann, Moon, LaPlante, Hu '062 and Gewirtz.

Hellmann's disclosure and the problem to be solved

Hellmann discloses an M13 construct with a Tobacco Vein Mottling Virus insert sequence, which is used to create DNA:RNA hybrid as used in an *in vitro* cell-free hybrid arrest assay. Hellmann is focused on developing an assay system to determine the origin of the polypeptide product encoded by the 5'- terminal region of the RNA of the potyvirus. Hellmann is further focused on precisely mapping the potyviral proteins and understanding the translational mechanisms by which they are produced. Hellmann states that single-stranded DNAs derived from plasmids containing approximately 95% of the sequences of TVMV RNA arrest the translation of specific portions of TVMV RNA and discovered that synthesis of P75 is initiated

near the 5' terminus (paragraph bridging pages 23-24). To solve the problem of understanding the translational mechanisms of potyvirus, Hellmann chose to employ a cell-free translation system using single-stranded DNA fragments obtained from M13, which contains the TVMV inserts because "initial attempts to perform hybrid-arrested translation experiments using double-stranded recombinant plasmids were unsuccessful due to rapid annealing of the DNA strands under the hybridization conditions use." (Page 25, paragraph bridging left and right columns).

Hellmann's research focus is on using a single-stranded DNA in cell-free hybrid arrested translation experiments because Hellmann is interested in the problem of solving the translational machinery of potyvirus for which the cell-free system is a more helpful experimental methodology than cell-based methodology. Accordingly, Hellmann fails to disclose or suggest transfecting any eukaryotic cell and therefore fails to disclose or suggest mixing its M13 molecule with a transfection agent.

Hellmann is not combinable with Moon, LaPlante, Hu '062, or Gewirtz

Applicants submit that the Hellmann reference and the Moon reference fail to be combinable with each other. The Moon reference discloses a composition that includes a 116-mer stem-loop DNA structure and a transfection effective carrier. Since Hellmann discloses only a cell-free system, with its own set of experimental challenges, there would be no reason for a person of ordinary skill in the art reviewing the Hellmann reference to consult the Moon reference directed to gene expression within a cell. Cell-free (Hellmann) and cell-based (Moon) systems each present separate, unique challenges. A person of skill in the art contemplating carrying out a cell-free based expression studies according to Hellmann would not look to a cell-

based gene expression system such as disclosed in Moon for guidance. Therefore, the Hellmann and Moon references are not analogous art and are not combinable.

Moreover, Moon states at page 4652, penultimate paragraph as follows:

> We used cationic liposomes to enhance the cellular uptake of RiAS oligos. From the experience of our own and other groups, a meaningful level of AS oligo uptake should be consistently obtainable when carried into cells by liposomes, regardless of the size of AS oligos (31, 32). Therefore, the relatively large size or RiAS oligos should not pose a problem for efficient cellular uptake. (emphasis added)

Moon suggests that the 116-mer oligonucleotide (RiAS) is relatively large, and that even this large an oligonucleotide should be able to be transfected into the cell. Moon considers 116-mer to be large. And yet makes no mention of the desirability or capability of transfecting a large circular single-stranded nucleic acid that is at least 3,000 bases long into a mammalian cell. Thus, it cannot be fairly said that the 116-mer transfection attained in Moon alone is suggestive of transfection effectiveness or desirability of a large circular single-stranded nucleic acid that is at least 3,000 bases long. Oligonucleotides, double stranded nucleic acids, linear nucleic acids, large circular single-stranded nucleic acids and so on are each biochemically, conformationally and sterically unique. There is a level of unpredictability as to how they would behave and whether they would be useful inside of a cell. Therefore, since Moon does not disclose or suggest transfection appropriate to the large circular single-stranded nucleic acid of the claimed invention, Moon fails to be applicable to the presently claimed invention.

LaPlante's disclosure of a human CHERP gene cDNA cloned into a plasmid and producing mRNA does not provide any motivation to transfect a large circular single-stranded nucleic acid molecule into a mammalian cell as in the claimed invention. LaPlante essentially discloses two types of nucleic acids – plasmid DNA and linear RNA. since LaPlante does not

disclose or suggest transfection appropriate to the large circular single-stranded nucleic acid of the claimed invention, LaPlante fails to be applicable to the presently claimed invention. Furthermore, Hellmann and LaPlante are again not combinable as references because they are in non-analogous art of cell-free and cell-based assay systems.

Applicants submit that the Hellmann reference and the Hu '062 patent fail to be combinable with each other. Hu '062 is firmly focused on inhibiting target gene expression by the expression of exogenously introduced plasmid DNA that expresses antisense RNA. Hu '062's research field is limited to the realm of transfecting cells, assaying for gene expression within a cell background, and assaying for changes in cell morphology. The methods and techniques employed richly revolve around cell cultures and assays using live organisms, which extend to therapeutics and treatment of disease, specifically AIDS. This is in stark contrast to the Hellmann reference, which is directed to a cell-free assay system that employs a single-stranded M13 phage construct to determine the translational mechanism of the potyvirus. Hellmann fails to disclose any information regarding any cell-based type of system. And a person in the art of target gene inhibition by expression of antisense RNA would not look to a cell-free assay system for guidance in solving its problems.

Since the purposes for which each reference uses either the single-stranded or double-stranded form of either the phage or the plasmid vector are divergent, a person of ordinary skill in the art reviewing the Hellmann reference would not be motivated to consider using a plasmid DNA expressing antisense RNA to assist in solving the hybridization problem discussed in the Hellmann reference. And *vice versa*, a person in the cell-based antisense therapy field would not be motivated to consider using a single-stranded M13 vector construct of Hellmann in solving its

therapeutic focus, as there is simply no motivation found in either reference to combine these references.

The Gewirtz reference discloses transfecting oligonucleotides and double stranded plasmid DNA into mammalian cells by complexing these types of nucleic acids with a transfection effective carrier. Gewirtz is concerned with better efficiency of oligonucleotides because this was the major focus of antisense research at the time. Transfection effective agents for nucleic acids were known in the art at the time of the invention as exemplified by Gewirtz. It is noted however that Gewirtz makes no mention expressly or impliedly that a large circular single-stranded nucleic acid as in the claimed invention may be transfected into eucaryotic cells. Furthermore, again as with the other cited references, the Gewirtz reference discloses a cell-based transfection oriented technology, which is not analogous to the cell-free system that Hellmann discloses. Therefore, these references fail to be combinable with each other.

Hindsight reconstruction

Applicants submit that the Examiner has cobbled together the cited five (5) references in an attempt to show obviousness of the claimed composition. The Examiner has cited these references with hindsight vision afforded by the claimed invention. Clearly, in order to establish obviousness of the claimed composition, it is not enough to show that each of the separate ingredients are in existence, as the Examiner has done. The Examiner must provide references that show the desirability and the motivation for combining the references to arrive at the claimed composition. All of the cited references fall short of this simply because none of the cited references recognizes or appreciates that the effective usefulness of transfecting these large circular single-stranded nucleic acid molecules into eucaryotic cells.

Indeed, Hellmann shows the opposite of the inventive concept because Hellmann shows a large circular single stranded nucleic acid molecule that is used in a cell-free system. Therefore, Hellmann certainly fails to provide any motivation to insert its nucleic acid into a eukaryotic cell, and further, Hellmann is not applicable to the cell-based transfection system of the claimed invention.

It must be appreciated that Applicants have at the time of the invention demonstrated for the first time that transfecting these large circular single-stranded nucleic acids into eukaryotic cells resulted in useful and effective antisense effects, which was not recognized before in the art because the art at the time was focused on injecting small oligonucleotides. No one had appreciated that a large circular single-stranded nucleic acid such as instantly claimed could be used to effect an antisense response.

There is no motivation found in the cited references to make the claimed composition

The Examiner's comments in the Office Action of July 13, 2005 have been noted. To summarize, the Examiner asserts that because it is known in the art that a closed circular approximately 120 nucleotide sequence can be transfected into eucaryotic cells (Moon); a plasmid DNA can be transfected into eucaryotic cells (LaPlante); a plasmid that expresses several target-specific antisense RNA can be transfected into eucaryotic cells (Hu); and generally, oligodeoxynucleotides and plasmid DNA can be mixed with lipid transfection agents (Gewirtz), it would have been obvious to mix the large circular single-stranded molecule disclosed in Hellmann with a transfection reagent at the time of the invention. In addition, the Examiner believes that a person of ordinary skill in the antisense art would understand that the transfection effective agents are commonly used with antisense nucleic acids. In essence, the Examiner

believes that all nucleic acids have similar properties, and therefore, if a eucaryotic transfection agent can be mixed with some of these types of nucleic acids, then the transfection agents can be mixed with the large circular single-stranded nucleic acid of the present invention as well.

Applicants disagree with the Examiner's analysis of the implications of the cited prior art and the reasons for the rejection. Applicants were the first to show that mixing the inventive large circular antisense nucleic acid molecule with a transfection effective reagent and transfecting the eucaryotic cell has the effect of ablating gene expression of the corresponding gene in the cell. Prior to Applicants' demonstration of this effect, there was no suggestion in the prior art that a large circular single-stranded nucleic acid as in the claimed invention was desirable for transfection into a eucaryotic cell to achieve any purpose at all. While double-stranded plasmids and oligonucleotide nucleic acids were known to be transfected into eucaryotic cells to achieve either therapeutic or other gene expression purposes, there was no motivation to insert a large circular single-stranded nucleic acid as in the claimed invention into eucaryotic cells.

The Examiner lumps all of the antisense molecules into one group and concludes that if some of these antisense molecules are known to be transfected into eucaryotic cells, then it would be obvious to mix the large circular antisense molecule of the present invention with a transfection agent for carrying out transfection into eucaryotic cells. However, Applicants note that not all antisense molecules are the same nor should they be lumped together into a single group. An oligonucleotide has unique properties, as does a double-stranded plasmid. In this regard, there has been no instance in the prior art that indicates a desirability of transfecting a single-stranded version of the large circular nucleic acid as in the claimed invention. Turning to

the Gewirtz reference for the moment, Applicants point to page 3161, far left column, last three sentences of the first paragraph, in which it is stated:

> A larger body of work has focused on the anti-mRNA or so-called "anti-sense" strategies, composed principally of the use of ribozymes and antisense oligodeoxynucleotides (AS ODNs). Antisense oligonucleotides have received the majority of attention because of their apparent ease of synthesis and use.

As can be seen in this passage, essentially there were two types of antisense strategies at the time of the invention—using the enzyme ribozyme, and using antisense oligonucleotides. The oligonucleotides were used mainly because of ease of synthesis. Because of the focus on the antisense oligonucleotides, a person of skill in the art of antisense therapy or diagnostics would be directed to antisense oligonucleotides and not to large circular single-stranded nucleic acid molecules as in the presently claimed invention for insertion into eucaryotic cells. Therefore, there is no reason at the time of the invention to mix a transfection reagent with the large circular single-stranded nucleic acid molecule of the invention because there is no desire, intent, or goal of inserting the inventive molecule into a eucaryotic cell. This is a significant point. If there is no motivation or directed reason to combine the particular type of compound of the instant claims with the transfection agent, then the composition as claimed cannot be held to be "obvious". This is so, especially in view of the state of the art at the time of the invention when it was thought that small oligonucleotides were most desirable for insertion into the eucaryotic cells. Thus, at a minimum, there was no motivation to insert the inventive compound into a eucaryotic cell. And further, it would be reasonable to conclude that a reference such as Gewirtz steers toward optimizing small oligonucleotide transfection, and therefore teaches away from using the inventive composition.

Applicants note that the large circular single-stranded nucleic acid of the invention cannot be grouped with the general antisense molecule that the Examiner appears to have categorized. Clearly, a double-stranded molecule has different properties from a single-stranded molecule. Even though they may possess nucleotide bases as the common unit components, the biochemical characterization of a single-stranded and double-stranded molecule reveal different results. Further, oligonucleotides in the range of 20 to 150, for instance, are not comparable to a large molecule that has over 3,000 bases. The molecular dynamics between these types of molecules are different. Just based on the sheer difference in size, a person of skill in the art would expect them to behave differently.

Applicants submit for the Examiner's consideration in support of the patentability of the presently claimed invention, a recently published article in *Nature Biotechnology* (Lee et al. "Gene knockdown by large circular antisense for high-throughput functional genomics", *Nature Biotechnology,* Vol. 23, No. 5, May 2005) by the inventors regarding the subject matter of the present application. *Nature Biotechnology* is one of the most prestigious journals in the field of biotechnology. Therefore, the subject matter of the claimed invention is acknowledged in scientific circles to be of significant advance over existing knowledge surrounding the antisense technology, fully supporting the non-obviousness of the presently claimed invention. Accordingly, the presently claimed invention is patentable over the cited references.

Response to Advisory Action of November 8, 2005

In the Advisory Action of November 8, 2005, the Examiner has stated essentially that while Examiner agrees that Applicants were the first to use the claimed antisense compound to demonstrate ablation in cells, mixing transfection agents with antisense compounds is already

known in the art and therefore the presently claimed invention directed to a composition comprising the antisense compound of the invention would have been obvious to a person of ordinary skill in the art.

In response, Applicants again stress that in the specific case of the large circular single-stranded nucleic acid molecule, there was no specific motivation to transfect this particular large circular single-stranded nucleic acid molecule into eukaryotic cells. One cannot simply assume that the use of a compound in a cell-free system automatically extends to its usefulness when transfected. It is obvious to try to do it, but in the absence of a specific motivation or teaching to carry out transfection, combining the molecule with a transfection agent for the purpose of transfecting into a cell must be considered to be non-obvious. Indeed, the primary reference Hellmann, which discloses the cell-free method, never discloses or suggests transfecting cells with its compound. Moreover, the recent Lee et al. paper, which was enclosed with the Applicants' previous response as evidence that transfection of the molecule unexpectedly resulted in gene expression ablation, was not previously considered by the Examiner. Applicants request the Examiner to review and consider this publication at this time.

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

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